Dual Effects of Neuroprotection and Neurotoxicity by General Anesthetics

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Surgery without Anesthesia

Original in the Royal College of Surgeons of England, London
Inhalational General Anesthetics

William T.G. Morton, First Ether Anesthesia, Oct. 16, 1846

Stoelting and Miller, Basics of Anesthesia, 2007
Anesthesia has been considered one of most advanced medicine in last century

More than 260 millions surgeries worldwide each year

6 millions pediatric anesthesia cases in US each year

General anesthetics were considered safe or even neuroprotective

General anesthetics may also be neurotoxic
Anaesthetic gas may damage brain cells
Widely-used compound may boost production of Alzheimer's protein.

Michael Hopkin

Los Angeles Times, May 14, 2007
By Chandra Shekhar

Anaesthesia: A medical mainstay re-examined
Some worry about brain cell death in studies of young animals. Human trials are planned.

News@Nature.Com
Published online: 6 February 2007;
doi:10.1038/news070205-4

Time Magazine
Anesthesia in Infancy Linked to Later Disabilities
By ALICE PARK Tuesday, Mar. 24, 2009
Evidence of General Anesthetics Mediated Neuroprotection
Anesthetic Neuroprotection: Tissue cultures

General anesthetics protect against neuronal cell damage induced by hypoxia, glutamate excitotoxicity.

General anesthetics protect against neuronal cell damage induced by oxygen-glucose deprivation (OGD, in vitro ischemia model).

General anesthetics protect against endotoxin-induced cell damage.

Neuroprotection of general anesthetics is dose- and time-dependent.
Anesthetic Neuroprotection: Animal Studies

General anesthetics protect against brain infarction induced by hypoxia, ischemia or hypoxia-ischemia

General anesthetics protect against traumatic brain injuries (TBI)

General anesthetics protects against ischemia injuries in heart, lung, kidney and liver

The potency of neuroprotection by various general anesthetics may be similar
Anesthetic Neuroprotection: Clinical studies

General anesthetics, especially isoflurane, reduces cardiac troponin I, acute myocardial infarction and death in CABG surgeries

Limitation in neuroprotection studies due to lack of reliable neurodegenerative biomarker and complexity of cognitive function tests

Further studies are needed to confirm the neuroprotection of general anesthetics in patients
Mechanisms of Cardioprotection by Volatile Anesthetics

Tanaka et al., Anesthesiology 2004; 100: 707-21
Are General Anesthetics Neuroprotective?

- Yes, in animal studies, but limited to mild or moderate brain damage from cerebral ischemia etc.

- Not sure in patients, although general anesthetics, especially isoflurane, provide effective cardiac protection.
Evidence of General Anesthetics Mediated Neurotoxicity
Anesthesia Neurotoxicity: Tissue cultures

General anesthetics induce damage in variety types of neurons and brain slices

Anesthetics neurotoxicity is dose-, time- and cell-dependent

Neurons featured with Alzheimer’s disease (AD) and Huntington’s disease (HD) seems to be more vulnerable to anesthesia toxicity
Anesthesia Neurotoxicity: Animal studies

General anesthetics induce widespread neurodegeneration in the fetus or newborn developing brains.

General anesthetic toxicity are dose-, time- and age-dependent.

General anesthetics cause persistent memory and learning impairment in animals.

General anesthetics increase plaque-load, neurodegeneration and aggregate cognitive dysfunction in the AD transgenetic mice.
Anesthesia Neurotoxicity: Clinical studies

Halothane: hepatotoxicity; Methoxyflurane: Renal toxicity

Link between exposure to anesthesia before 3 years old and later behavioral and developmental disorders

Duration of Anesthesia is a risk factor for short term post operative cognitive dysfunction (POCD)

Inverse relationship between surgical experience and age of onset of AD

Anesthesia unmask symptoms of Parkinson’s disease

Anesthesiologists were more likely to die from Parkinson’s disease than age-matched internists
Are General Anesthetics Neurotoxic to Developing Brains?
Propofol Induces Apoptosis in Mouse Newborn Developing Brain

Cattano et al., Anesth Analg 2008; 106: 1712-4
Ketamine Induces Apoptosis in Monkey Developing Brain Time-Dependently

Zou et al., Int J Dev Neurosci 2009; 27: 727-31
Isoflurane Causes Greater Neurodegeneration than Sevoflurane in Developing Brains

Liang et al., Anesthesiology 2010; 112: 1325-34
Early Multiple Anesthesia Exposure is Associated with later Learning Disability

- 5,357 children (593 received GA before age 4)
- Learning – IQ and Achievement tests
- Single exposure – no increased risk
- Multiple exposures increase learning disability

Wilder et al., Anesthesiology 2009; 110: 796-804
Limited Clinical Data on Anesthetic Neurotoxicity in the Developing Brains in Pediatric Patients

### Table 2: Summary of clinical studies related to anaesthetic neurotoxicity

<table>
<thead>
<tr>
<th>Neurocognitive outcome</th>
<th>Assessment tools</th>
<th>Study details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learning disability (in language or math or reading)</td>
<td>Learning Disability criteria (based on IQ and achievement test results)</td>
<td>Olmstead County Birth Cohort(^{22, 29})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Findings: multiple exposure increases risk for learning disability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Findings: there is no difference in incidence of learning disability between children whose mother had Caesarean section under general anaesthesia and regional anaesthesia</td>
</tr>
<tr>
<td>Behaviour</td>
<td>Child Behavior Checklist (CBCL)</td>
<td>Retrospective ‘pilot’ study in urology patients aged 0–6 yr.(^{21}) Underpowered</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Findings: trend towards more atypical behaviour with exposure NYS Medicaid data set(^{20})</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>ICD-9 diagnosis codes</td>
<td>Findings: hernia under 36 months of age increases risks for developmental disorder</td>
</tr>
<tr>
<td>Behavioural problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autism spectrum disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education achievement</td>
<td>Dutch CITO-elementary test-cognitive problems/inattention subscale of Conner’s Teacher Rating Scale: short form</td>
<td>Young-Netherlands Twin Register(^{19})</td>
</tr>
<tr>
<td>Teacher rating of behaviour</td>
<td></td>
<td>Findings: no differences in twins discordant for anaesthesia exposure before 36 months</td>
</tr>
</tbody>
</table>
Ongoing Large-Scale Multiple Centers Prospective Clinical Trials

- **GAS Study:**
  
  600 infants, sevoflurane vs. regional anesthesia for inguinal hernia repair, Neuropsychological test at 2, 5 years for developmental and learning disorder.

- **PANDA (Pediatric Anesthesia and NeuroDevelopment Assessment) Study:**

  500 sibling pairs younger than 3 years old, single general anesthesia for inguinal hernia repair vs. no anesthesia, Neuropsychological tests for developmental or learning disorder between 8 and 15 years old.

Sun, Brit J Anaesth 2010; 105: i61-i68
Are General Anesthetics Neurotoxic to Developing Brains?

- Yes, in animal studies
- Not clear at present, in pediatric patients
Do General Anesthetics Contribute to Postoperative Cognitive Dysfunction (POCD)?

Common anecdote:

“My father (grandfather, uncle, mother, brother, etc.) has never been the same after his surgery”
Postoperative Cognitive Dysfunction (POCD)

- Poorly defined and diagnosed

- Persistent POCD is considered if duration is longer than 6 months

- Incidence of POCD may varies, depending the methods and the time of monitoring POCD

- Multiple risk factors, with advanced age a major risk factor. Other proposed risk factors: major cardiac (CABG) or orthopedic surgeries, microemboli, hypoxia and ischemia, infection, respiratory complication etc.

- Persistent POCD increase perioperative mortality and is a major health problem
Proposed Contribution of Anesthesia or Surgery to Postoperative Cognitive Dysfunction (POCD)

Borsook et al., Prog Neurobiol 2010; 92; 601-12
Age Is the Only Risk Factor for POCD at 3 Months After Surgery

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>1 week</th>
<th></th>
<th>3 months</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Patients</td>
<td>Number</td>
<td>Patients</td>
</tr>
<tr>
<td></td>
<td>of patients</td>
<td>with POCD</td>
<td>of patients</td>
<td>with POCD</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>586</td>
<td>135 (23%)</td>
<td>532</td>
<td>37 (7%)</td>
</tr>
<tr>
<td>≥70</td>
<td>425</td>
<td>123 (29%)</td>
<td>378</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Complication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoxaemia*</td>
<td>115</td>
<td>30 (26%)</td>
<td>98</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>Hypotension†</td>
<td>229</td>
<td>60 (26%)</td>
<td>214</td>
<td>51 (9%)</td>
</tr>
<tr>
<td>Respiratory complication</td>
<td>99</td>
<td>40 (40%)</td>
<td>88</td>
<td>12 (14%)</td>
</tr>
<tr>
<td>Infectious complication</td>
<td>91</td>
<td>30 (33%)</td>
<td>138</td>
<td>12 (9%)</td>
</tr>
<tr>
<td>Second operation</td>
<td>24</td>
<td>13 (54%)</td>
<td>50</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤120</td>
<td>196</td>
<td>35 (18%)</td>
<td>179</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>121–240</td>
<td>503</td>
<td>121 (24%)</td>
<td>448</td>
<td>40 (9%)</td>
</tr>
<tr>
<td>≥241</td>
<td>312</td>
<td>103 (33%)</td>
<td>283</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>576</td>
<td>156 (27%)</td>
<td>518</td>
<td>47 (9%)</td>
</tr>
<tr>
<td>High school</td>
<td>290</td>
<td>75 (26%)</td>
<td>260</td>
<td>26 (10%)</td>
</tr>
<tr>
<td>More than high school</td>
<td>145</td>
<td>31 (21%)</td>
<td>132</td>
<td>16 (12%)</td>
</tr>
<tr>
<td>Benzodiazepines before surgery</td>
<td>116</td>
<td>33 (28%)</td>
<td>105</td>
<td>5 (5%)</td>
</tr>
</tbody>
</table>

POCD = postoperative cognitive dysfunction.
*One or more episodes of oxygen saturation ≤80% for ≥2 min.
†One or more episodes of mean arterial pressure ≤60% for ≥30 min.

Table 3: Proportion of patients with postoperative cognitive dysfunction at 1 week and 3 months by risk factor

Moller et al., Lancet 1998; 351: 857-61
Do General Anesthetics Contribute to Postoperative Cognitive Dysfunction (POCD)?

Not enough evidence at present support the contribution of anesthesia to the development of persistent POCD in patients.
Proposed Mechanisms for Anesthesia Neurotoxicity

- GABA receptor activation: Excitotoxicity in the developing brains
- NMDA receptor antagonism: Withdraw of trophic factors in the developing brains
- Increased β-amyloid production and aggregation: Alzheimer pathology
- L-carnitine, melatonin, lithium, inhibition of P75 neurotrophin receptor, free radical scavanger can ameliorate general anesthetic toxicity
- Disruption of intracellular calcium homeostasis: General underlying mechanism?
Roles of Calcium Dysregulation in Anesthetics Mediated Neurotoxicity

Wei, Anesth Analg 2011: 113: 972-4
Anesthetics Induce Neuronal Apoptosis by Causing Abnormal Calcium Release via Over Activation of InsP$_3$R

Wei et al., Anesthesiology 2008; 108: 251-60

Zhao et al., J Pharmacol Exp Ther 2010; 333:14-22
Isoflurane Modulate InsP$_3$R Calcium Channel Opening

DT40 chicken lymphocyte nucleus with type 3 IP$_3$R

Peng et al., Neuroscience Meeting, Chicago, 2009
Propofol Modulates InsP$_3$R Calcium Channel Opening

DT40 chicken lymphocyte nucleus with type 1 or 3 IP$_3$R

Peng et al., Neuroscience Meeting, Washington DC, 2011
Are General Anesthetics Neuroprotective or Neurotoxic?
Dual Effects of Anesthetics Neuroprotection or Neurotoxicity via Modulation of InsP$_3$R

Inan and Wei, In Review, Br J Anaesth 2011
Isoflurane Provides Preconditioning and Neuroprotection via Moderating Activation of InsP$_3$R

Gray et al., Anesthesiology 2005; 102: 606-15
General Anesthetics Are Both Neuroprotective and Neurotoxic, Depending on the Duration of Treatment

PC12 cells with AD Presenilin-1 mutation, General Anesthetics Preconditioning 1 hr, then Isoflurane Neurotoxicity 24 hr

Wei et al., Neurosci Lett 2007; 425: 59-62
Isoflurane Is Both Neuroprotective and Neurotoxic in the Rat Developing Brain, Depending on the Duration of Treatment

7-day-old rats, Preconditioning: 1.5% isoflurane 0.5 hr; Neurotoxicity: 1.5% isoflurane 6 hr

Peng et al., Neuroscience Meeting, San Diego, CA, 2010
1.3% Isoflurane Inhibits Spontaneous Neuronal Apoptosis in Rat Fetus Developing Brains and Improve Postnatal Memory

Pregnant rats, 1.3% isoflurane for 6 hr, fetus brain caspase-3 immunostaining, postnatal memory and learning with MWM

Li et al., Neuropharmacology 2007; 53: 942-50
3% Isoflurane Promotes Neuronal Apoptosis in Rat Fetus Developing Brains

Pregnant rats, 1.3% or 3% isoflurane for 1 hr, fetus developing brain neurodegeneration

Dual Effects of Neuroprotection and Neurotoxicity by General Anesthetics

Zhao et al, Anesthesiology Accepted, 2012
Minimal Exposure of Isoflurane Inhibits Neuronal Stem Cell death Induced By Excessive Exposure of Isoflurane

Zhao et al, Anesthesiology Accepted, 2012
Preconditioning with Minimal Exposure of Isoflurane Inhibits abnormal elevation of \([\text{Ca}^{2+}]_c\) Induced By Excessive Exposure of Isoflurane

Zhao et al, Anesthesiology Accepted, 2012
Minimal Exposure of Isoflurane Ameliorates the Inhibition of Neuronal Stem Cell Proliferation Induced By Excessive Exposure of Isoflurane

Zhao et al, Anesthesiology, Accepted, 2012
Short Exposure of Isoflurane Ameliorates the Inhibition of Human Neuronal Stem Cell Differentiation Induced By Prolonged Exposure of Isoflurane

Zhao et al, Anesthesiology, Accepted, 2012
Preconditioning Induces Endogenous Neuroprotective Mechanisms

Dirnagl et al., Trends Neurosci 2003; 26: 248-54
Are General Anesthetics Neuroprotective or Neurotoxic?

- General anesthetics are both neuroprotective and neurotoxic, depending on anesthetic concentrations and anesthesia duration.

- Isoflurane and propofol alone can modulate InsP$_3$R calcium channel opening.

- Activation of InsP$_3$R and/or RYR plays an important role on general anesthetics mediated neuroprotection and neurotoxicity.
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